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Submitted to: *amber.daniel@inotivco.com*
Re: Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies (88 Fed. Reg. 54342 August 10, 2023).

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Dear Dr. Kleinstreuer:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments on the Draft Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup entitled "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies."[2] The activities of ICCVAM, and others in the regulatory science community, to address the needs to articulate in greater detail approaches for Fit-For-Purpose Validation of New Approach Methodologies (NAMs) is an important step. This will help ensure there is sufficient scientific confidence in NAMs as they move from developmental phases to application in regulatory decision making and product stewardship actions.

For more than 10 years, ACC has been constructively engaged in developing NAMs through the ACC Long-Range Research Initiative (LRI), and developing and demonstrating, through proof of concept applications, procedures to actualize a robust, but flexible, Scientific Confidence Framework (SCF) for fit-for-purpose (FFP) validation of NAMs (see, for example, recent publications in the ACC LRI Research Catalog).[3]

In the comments that follow, we offer several suggestions / recommendations for improving the Draft ICCVAM Report. Should you have any questions on these comments and recommendations, please contact Rick Becker (Rick_Becker@americanchemistry.com) or

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

[2] https://ntp.niehs.nih.gov/sites/default/files/2023-08/VWG%20Report%20Draft_for%20public%20comment_08Aug2023.pdf

[3] https://lri.americanchemistry.com/

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Regards,

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General Comments

1. Key Components of a Scientific Confidence Framework

Over the last year or two, scientists in the regulatory science communities have started to converge on key components of FFP validation of NAMs. The key question that must be addressed in these FFP validation approaches for NAMs is, "*What does it take to achieve the requisite degree of scientific confidence in a NAM for its use in specific applications*?"

To this end, ACC has developed a seven-step Scientific Confidence Framework (SCF)[4] for NAMs, described in outline form below. This SCF is similar to the framework recently published by Parish et al 2020[5] (HESI) and van der Zalm et al (2022).[6] The key differences are that the ACC SCF 1) elevates the performance of the inference model to a separate step and 2) includes a specific justification narrative as a separate step so that the analysis that shows there is sufficient confidence to support use of the NAM for a specific decision context is clearly communicated (see Table 1).

Table 1.ACC Recommended Steps to be Included in a Scientific Confidence Framework for NAMs (Key Difference from Other SCFs are in Red)
Step 1. Intended Applications and Decision Context of Use (Hypothesis): Description of the proposed use & the specific decision for which the results will be used
Step 2: Biological Relevance: Description of the biological relevance of the NAM based on knowledge of how the NAM is linked to the system (e.g., biological pathway, AOP, etc.) of interest
Step 3: Analytical Validation: Documentation of assay sensitivity, specificity, reliability, and domain of applicability
Step 4: Evaluation of the Performance of the Inference Model: Documentation of inference (prediction) models based on the response-response relationships. (Performance characteristics in using the NAM response to predict/ infer the response of interest (e.g., toxicity end points))
Step 5. Transparency: Dissemination of the data, inference models, etc. in such a manner that an expert could independently replicate the analyses and documentation of previous independent scientific peer review(s).

[4] Ryman-Rasmussen, 2023. A Widely Applicable Framework for Establishing Scientific Confidence in NAMs. The Toxicologist (Supplement to Toxicological Sciences), ISSN 1096-6080 Volume 192, Issue S1 March 2023; page 29. https://www.toxicology.org/pubs/docs/Tox/2023Tox.pdf.

[5] Parish et al., 2020. An evaluation framework for new approach methodologies (NAMs) for human health safety assessment. Regul Toxicol Pharmacol. 2020 Apr;112:104592. doi: 10.1016/j.yrtph.2020.104592. Epub 2020 Feb 1. PMID: 32017962.

[6] van der Zalm, et al., 2022. A framework for establishing scientific confidence in new approach methodologies. Arch Toxicol. 2022 Nov;96(11):2865-2879. doi: 10.1007/s00204-022-03365-4. Epub 2022 Aug 20. PMID: 35987941; PMCID: PMC9525335.

Step 6. Justification Narrative: Written narrative explaining why there is sufficient scientific confidence in the NAM to support the specific decisions for the intended applications.
Step 7. Independent Review: Scientific peer review of Steps 1-6.

2. *Procedures Should be Developed for Receiving (and Evaluating) Nominations of NAMs for Readiness to Be Used*

The development of NAMs is proceeding at considerable speed in government labs, academia, and the private sector. To accelerate the uptake and use of NAMs in product stewardship, regulatory evaluations, and decision making, ICCVAM agencies (particularly EPA) need to develop a procedure for receiving and evaluating nominations for NAMs for specific decision contexts. Such a process should provide a specific and detailed uniform template for submitters to organize the information, data, analyses and narrative justification documenting the scientific confidence in the NAM for its proposed use. We recommend agencies consider adopting the steps of the ACC SCF framework outlined above.

In addition, agencies should incorporate best practices for stakeholder involvement, such as public meetings / workshops, formal public comment periods, and transparent communication of responses to peer review and public comments. This is particularly important for EPA because of the requirements in TSCA § 4 that the EPA Administrator develop "a list, which the Administrator shall update on a regular basis, of particular alternative test methods or strategies the Administrator has identified that do not require new vertebrate animal testing and are scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing."[7]

3. *The Term "Intended Applications and Decision Context of Use" should replace the term "Conditions of Use."*

Throughout the Draft ICCVAM Report, the term "Conditions of Use" is used to make the point that the development and communication of scientific confidence in a NAM needs to be linked to the regulatory decision context for which the NAM is proposed to be used. ACC agrees that a NAM needs to be evaluated specifically for each intended use. However, the term "conditions of use" should not be used here, for two reasons.

First, "conditions of use" is defined in TSCA as "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be

[7] 15 U.S.C. § 2603(h)(2)(C).

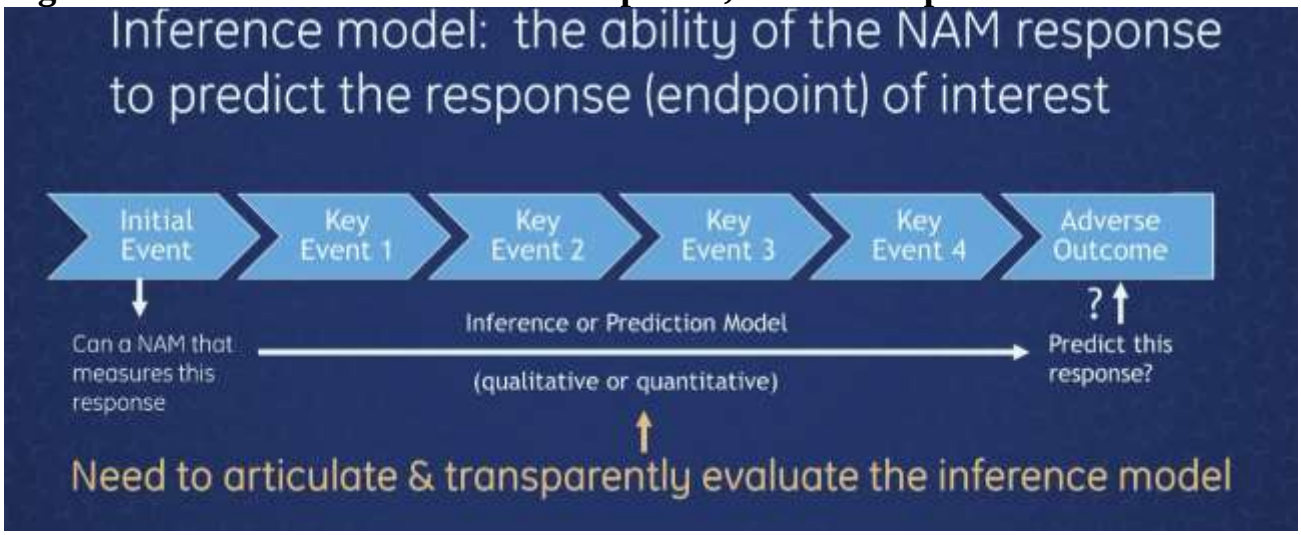
manufactured, processed, distributed in commerce, used, or disposed of."[8]

Second, the term we recommend, "Intended Applications and Decision Context of Use," is more precise because it links "application" of the NAM to the "decision context" for which it is to be used. As an example, for the ER Pathway Model (which uses binding and ER transactivation assay data) developed by EPA for use in the EDSP,[9] the "intended application" would be to "screen substances for estrogenic activity in lieu of conducting the in vivo uterotrophic assay" and the "decision context of use" would be to "identify substances with estrogenic activity for weight of the evidence analysis to determine the need for further testing to characterize the in vivo dose-response relationship for adverse effects."

4. Inference Model Performance Should Be a Stand-Alone, Key Analysis Component of the Scientific Confidence Framework.

The Draft ICCVAM Report correctly states that key concepts "involved in that flexible, fit-for-purpose validation process are biological relevance, technical characterization, data integrity, and information transparency." Characterization of the performance of the inference model seems to be implied as a step within the concept of "technical characterization." However, inference model performance is so critical to establishing the confidence of a NAM for a specific intended application and decision context of use that inference model performance should be a stand-alone key analysis step. As depicted in Figure 1, the inference model is the ability of the NAM response to predict the response (endpoint) of interest. Accordingly, there is a critical need to separately articulate and transparently evaluate the inference model.

Figure 1: The Inference Model as a Separate, Critical Step



[8] 15 U.S.C. §2602(4).
[9] Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP), December 13, 2022. https://downloads.regulations.gov/EPA-HQ-OPP-2021-0756-0002/content.pdf.

5. *The "Justification Narrative" (Step 6 in Table 1) Should be Used to Address the Sufficiency of the NAM to Underpin the Decision.*

Page 6 of the Draft ICCVAM Report states: "Specifically there should be evidence to support that the use of an alternative method will lead a regulatory review to the same or more protective decision as the reviewer would make based on existing methods." This type of blanket statement has very little meaning. Any NAM method that "predicted" a lower value than the current method could then be deemed sufficient. This would be unscientific. Biological relevance is key here in order to avoid unscientific and arbitrary risk assessments.

For example, in evaluating the carcinogenic potential of a substance, one might apply a NAM (or an IATA composed of NAMs). To do this, one would want to use knowledge of cancer modes of action (MOAs)[10] to identify the most likely operative MOA. One would then set a regulatory health-based guidance value that is protective of that chemical operating through that specific MOA to induce an adverse effect. If one determines, using a NAM (or IATA), that a substance's likely carcinogenic MOA is cytotoxicity resulting in compensatory cell proliferation that, at a sufficient magnitude and duration, can evolve into a neoplasm, the resulting health-based guidance value derived from a NAM-based cytotoxicity POD from ToxCast data would be biologically relevant. However, it would certainly not be as health protective as if one instead invoked, for "precautionary" reasons, a linear low dose, no threshold mutagenic MOA assumption. Similarly, if a NAM method were determined to predict that the potency of a substance (such as genistein) to interact with the estrogen pathway is orders of magnitude lower than the existing method indicates, it would be inappropriate to adopt and use that NAM just because this "alternative" method was "more protective." Thus, it is not only the protectiveness of the NAM that is important, but also the ability of the NAM to predict a biologically relevant effect. Again, this points to the need for including the Inference Model Performance Analysis as a keystone component of the Scientific Confidence Framework.

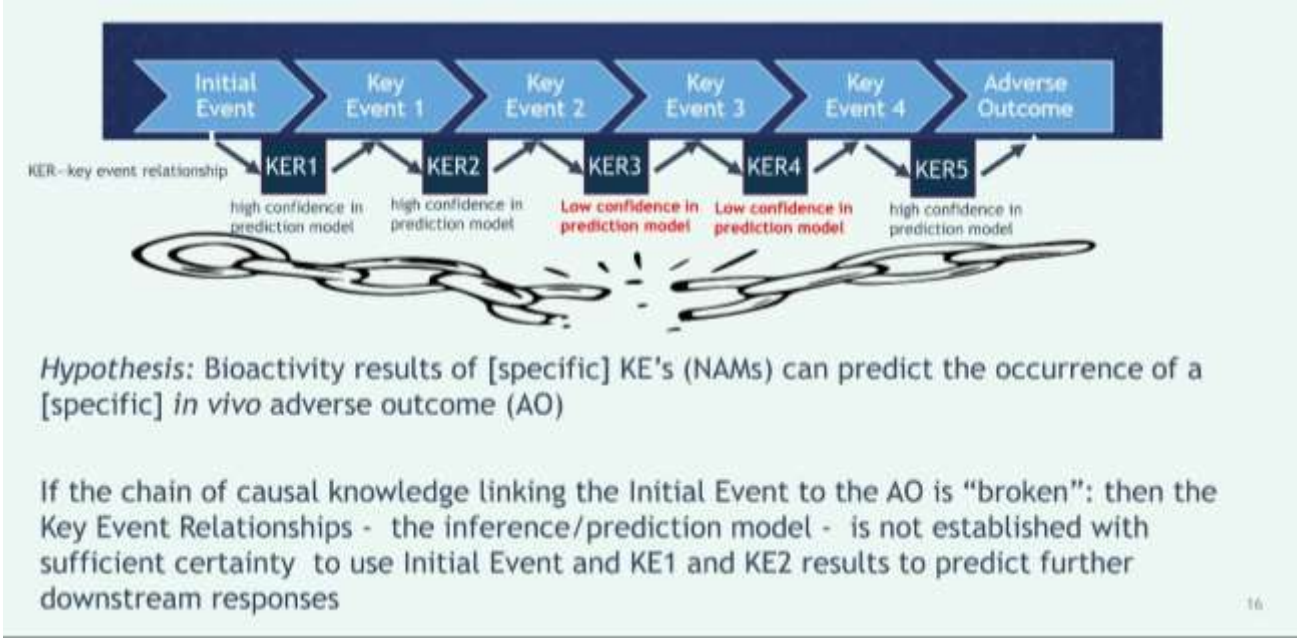
6. *"Evaluation of the Performance of the Inference Model" and "Justification Narrative" are Still Necessary, Even when Comparison to Data from Traditional Animal Test Methods May not be Possible.*

In the absence of data from traditional animal studies to use for evaluating a NAM, one will need to rely heavily upon knowledge of molecular structures, QSARs, biological pathways etc. Nevertheless, even in these cases, the inference model should be articulated and rigorously

[10] Wolf, et al., 2019. Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. Regulatory Toxicology and Pharmacology. 103. 10.1016/j.yrtph.2019.01.021.

evaluated, and the justification narrative completed. For example, one cannot simply assert that a NAM that evaluates an endpoint for which there is no existing animal model or animal data can be used straight away to set a regulatory value. Instead, the case must be made that the NAM produces results of sufficient scientific quality and confidence that one can reliably infer the NAM predicts the adverse effect of concern. In such a case, an adverse outcome pathway (AOP) analysis approach may be useful. However, even with an AOP, one must have sufficient confidence that an upstream Key Event can predict a downstream Key Event. If the confidence in one or more Key Event Relationship is low, the causal chain linking early Key Events to the Adverse Outcome may be broken. When linkages in the chain of causality are broken, one cannot infer an AO based upon the earlier KEs. This is illustrated in Figure 2 (adapted from Patlewicz et al., 2015).[11]

Figure 2. Causal Linkages in an Adverse Outcome Pathway to an Adverse Outcome. An Adverse Outcome is not Supportable when Links in the Chain of Causality are Broken.



[11] Patlewicz et al., 2015. Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. Regul Toxicol Pharmacol. 2015 Apr;71(3):463-77. doi: 10.1016/j.yrtph.2015.02.011. Epub 2015 Feb 20. PMID: 25707856